

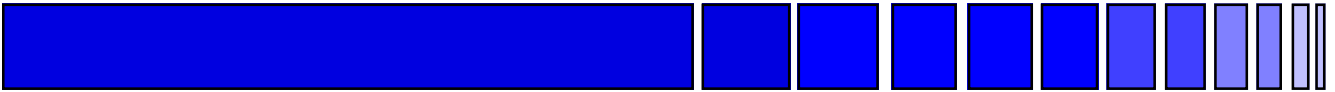
**CECAM workshop, "Implicit solvent  
models for biomolecular simulations,"  
Ecole Normale Supérieure, Lyon,  
11-14 May 1998**



# **Hydration and Quasi- Chemical Theories of Associated Liquids**

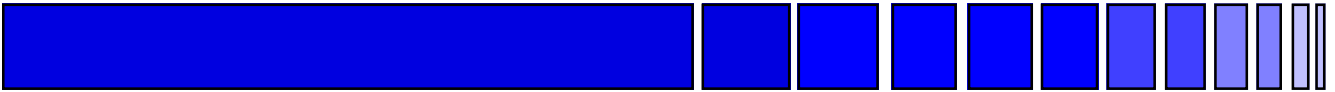
**L. R. Pratt, G. Hummer,  
A. E. Garcia, and R. A. LaViolette**

# General Issues

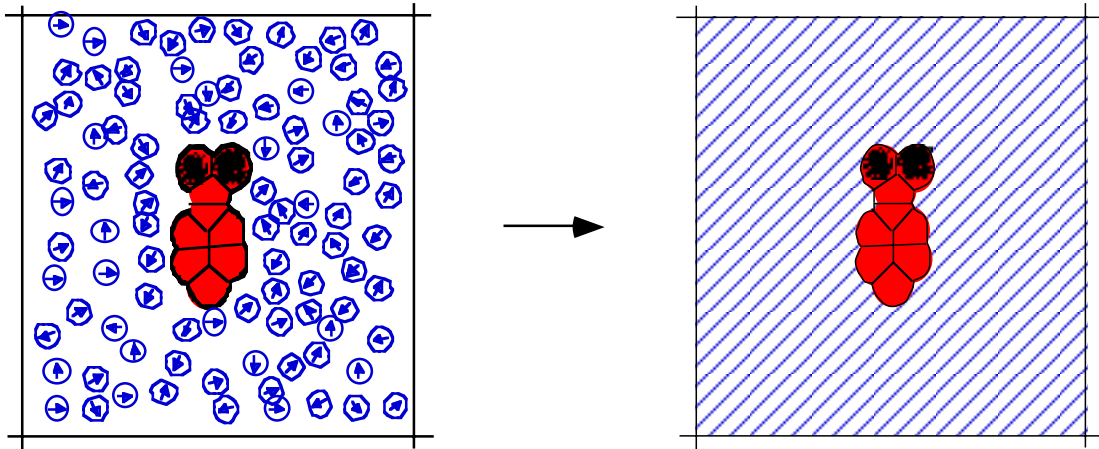


- **What questions are asked?**  
**Structure, dynamics, chemistry of biomolecular solutes?**
- **Formalities are clear - “integrate-out those degrees of freedom” - but not directly helpful.**
- **Solvents generally? Or dilute aqueous solutions? Or Water?**
- **A range of thermodynamic states (T,p,x)?**
- **All types of medium effects? Or Hydrophobic & hydrophilic & salt effects?**

# Dielectric Model

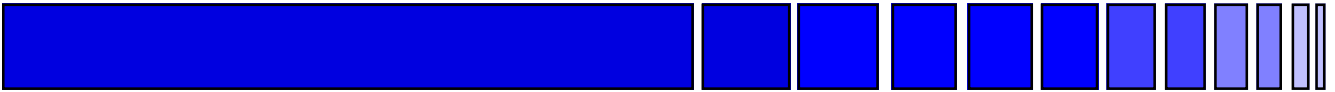


■ premier example of an “implicit water model.”



$$\nabla \bullet \boldsymbol{\epsilon}(\mathbf{r}) \nabla \Phi(\mathbf{r}) = -4\pi \boldsymbol{\rho}(\mathbf{r})$$

# Dielectric Model



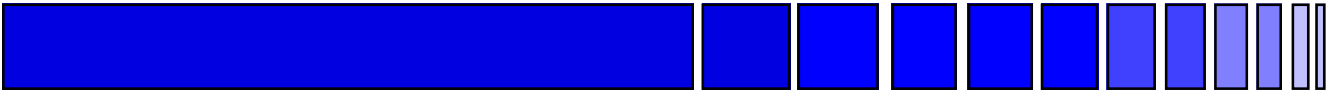
## ■ pro:

- **physical** - can be derived from a Hamiltonian.  
(in more than one way!)
- **practical** - reasonably treats huge effects that can't be ignored
- **chemical** - can simultaneously include reasonable chemistry
- **empirical** - parameterizations (radii) are not unreasonable

## ■ con:

- careful, molecular scale validation is **MIXED**
- often **100% empirical** - parameters (radii) must be reconsidered for **EVERY** new result; results are sensitive to parameters and any physical result (correct or not) can be reproduced

“Text for ...”



■ **“Everything should be made as simple as possible, but no simpler.”  
A. Einstein**

■ **Hydrophilic (electrostatic)**

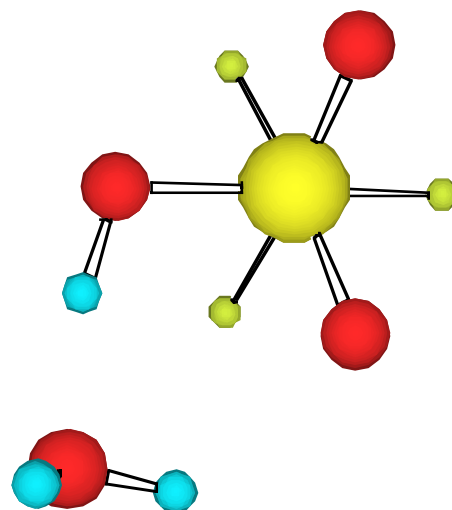
- “Molecular theories and simulation of ions and polar molecules in water,” Hummer, Pratt, & Garcia, LA-UR-98-1947.
  - » electrostatic interactions & the thermodynamic limit: “*Ewald is an easy way to get it right.*”
  - » physical conclusions: how, where do dielectric models really fail.
  - » theories: perturbation theory, multi-gaussian, quasi-chemical
- “Quasi-chemical theories of associated liquids,” Pratt & LaViolette, LA-UR-98-991 (*Molec. Phys.* 1998 in press)
  - » genesis: Guggenheim, Bethe (1935) and cooperative phenomena
  - » theoretical program for inclusion of chemistry in hydration of biomolecules

# Physical conclusions from simulations

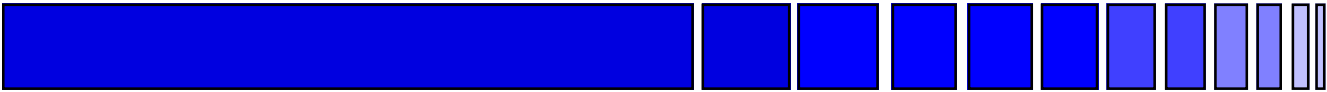


## ■ Dielectric models of hydration fail on a molecular scale when proton (H) structures near the solute lead to non-gaussian fluctuations of electrostatic potentials

- easiest examples to get “right” are classic cations, *e.g.*  $\text{Na}^+$
- neutral, polar, H-bonding molecules, *e.g.*  $\text{H}_2\text{O}$  or imidazole are more difficult cases for dielectric models when tested on a molecular scale. However, hydration free energies are smaller than for ions.
- negative ions are again a problem and the hydration free energies will be large. But here chemistry will be more important also for negative ions of first importance, *e.g.*  $\text{HCO}_3^-$ .



# How to test?



## ■ Dielectric models are simplified ...

- second order perturbation theory,
- or (equivalently) linear response,
- or (equivalently) gaussian fluctuation of electrostatic potentials.

## ■ For a spherical ion

- Born model

$$\Delta\mu = -\frac{q^2}{2R}\left(\frac{\varepsilon - 1}{\varepsilon}\right)$$

- second order perturbation theory

$$\Delta\mu = \Delta\mu_0 + q\langle\Phi\rangle_0 - \frac{\beta q^2}{2}\langle\delta\Phi^2\rangle_0$$

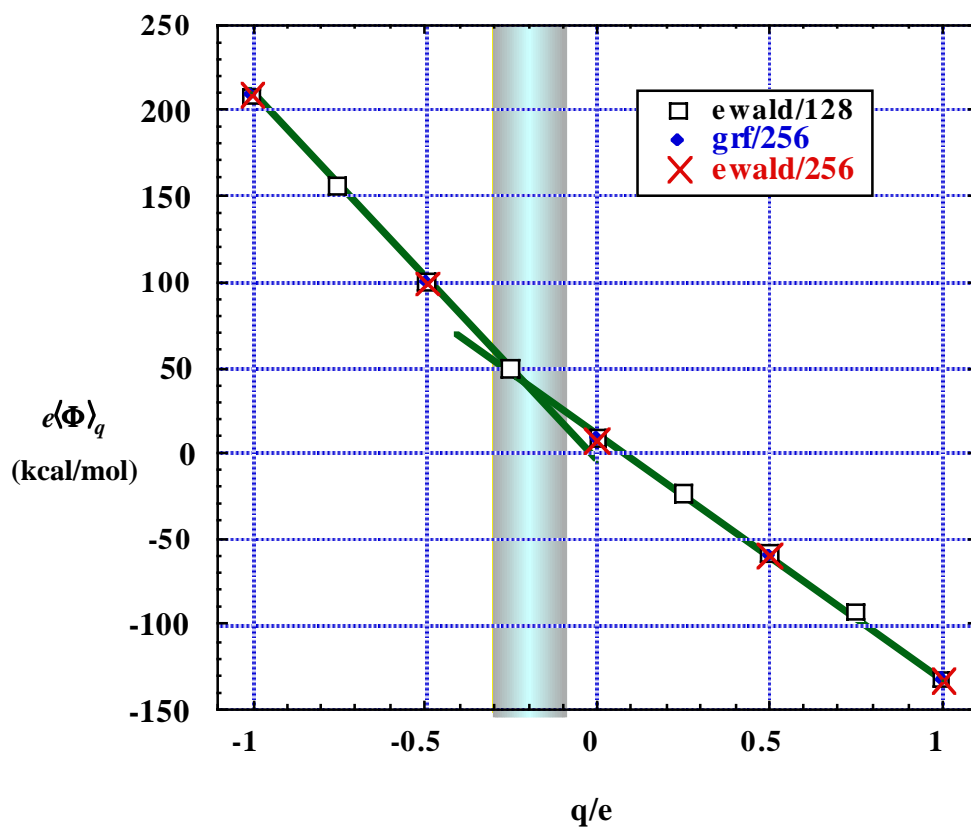
## ■ Test those approaches and avoid the issue of empirical adjustment of radii.

# Specific examples



## ■ charging of spherical ions

- “Free energy of ionic hydration,” Hummer, Pratt, & Garcia, *J. Phys. Chem.* 100, 1206 (1996).



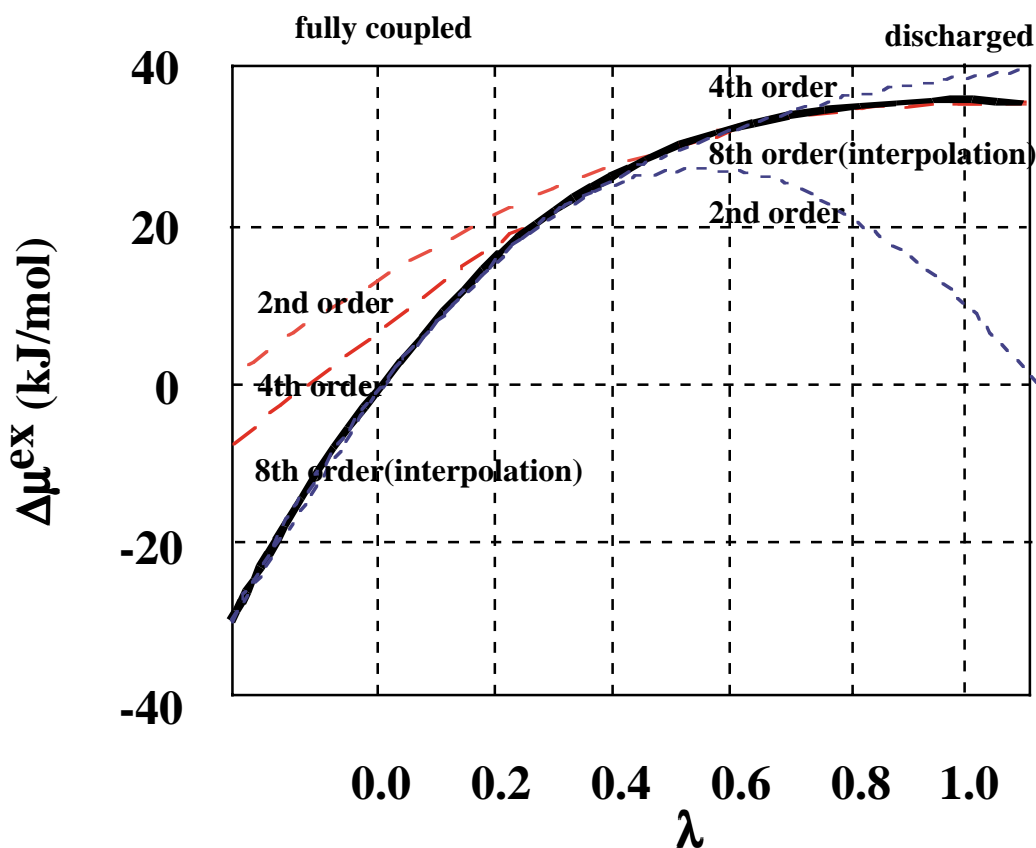


# specific examples



## ■ water in water

- SPC model water, Rick & Berne (1994) + “Hydration free energy of water,” Hummer, Pratt, & Garcia *J. Phys. Chem.* 99, 14188 (1995), accurate agreement



**Fix it**



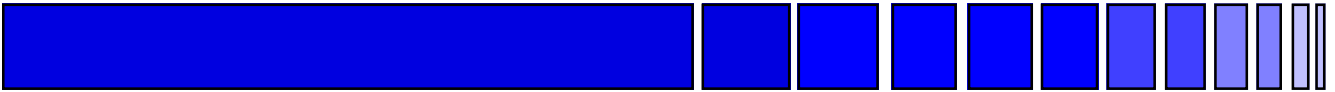
## ■ Conformational substates

- gaussian model for each substate:  
“Multistate gaussian model for electrostatic solvation free energies,” Hummer, Pratt, & Garcia, *J. Am. Chem. Soc.* 119, 8523 (1997)
- Not “dielectric saturation and electrostriction;” incrementally higher perturbation theory not that helpful - kinks!
- substates are categorized by numbers of close H-bonds to solute.

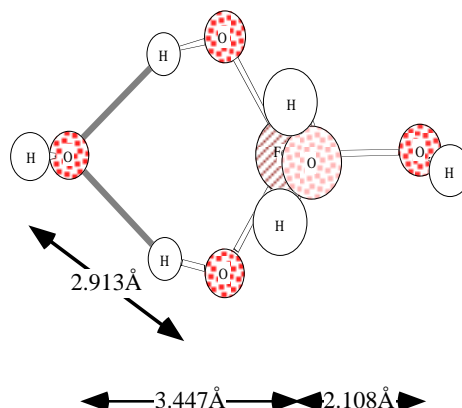
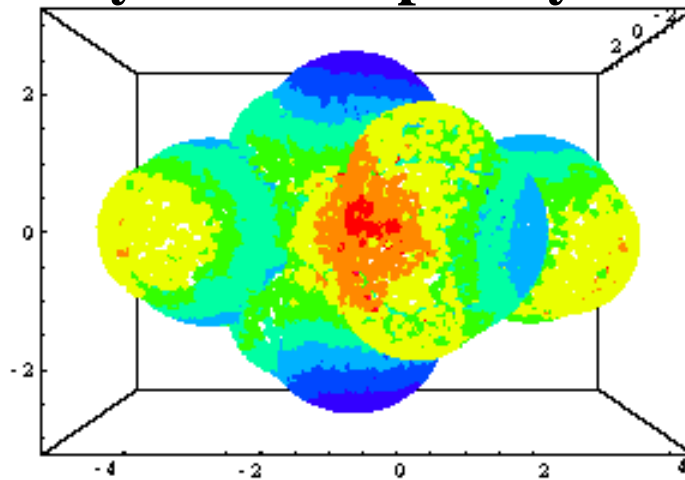
$$\beta\Delta\mu(\lambda) = -\ln \sum_n w_n e^{-\beta\lambda m_n + (\beta\lambda\sigma_n)^2/2}$$

- water:  $w_n$ ,  $1 \leq n \leq 6$ ,  $\langle n \rangle = 3.64$ , remaining max{error} about 5%.
- negative ions, *e.g.*,  $\text{Cl}^-$ , still a problem.

# Quasi-chemical



- yet need a way to start with non-simulation theory, include chemistry and calculate
- Chemistry - it'll surprise you.



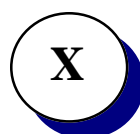
# Specific example



## ■ Absolute hydration free energy of the $\text{Fe}^{3+} (aq)$ ion

- experiment:  $\{-1019, -1039\}$  kcal/mol
- calculation: -1020 kcal/mol [“Hydrolysis of ferric ion in water and conformational equilibrium,” Martin, Hay, & Pratt, LA-UR-97-3489, (*J. Phys. Chem A* in press 1998)]



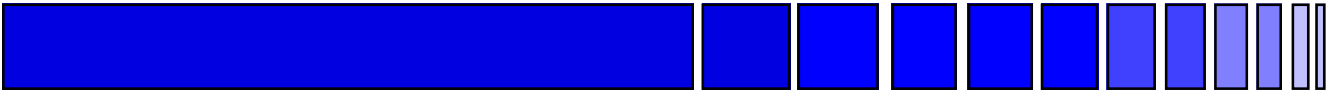

 $6 \mu_{\text{ligand}} ("p=1354 \text{ atm}") \Delta \mu_{\text{complex}}$

$$\begin{aligned}
 \Delta \mu_{\text{Fe}^{3+}} &= -RT \ln K_6 + \Delta \mu_{\text{complex}} - 6 \mu_{\text{ligand}} \\
 &= -RT \ln \left[ K_6 \left( \frac{\rho_{\text{ligand}} RT}{1 \text{ atm}} \right)^6 \right] \\
 &\quad + \Delta \mu_{\text{complex}} - 6 \Delta \mu_{\text{ligand}}
 \end{aligned}$$

-629 kcal/mol

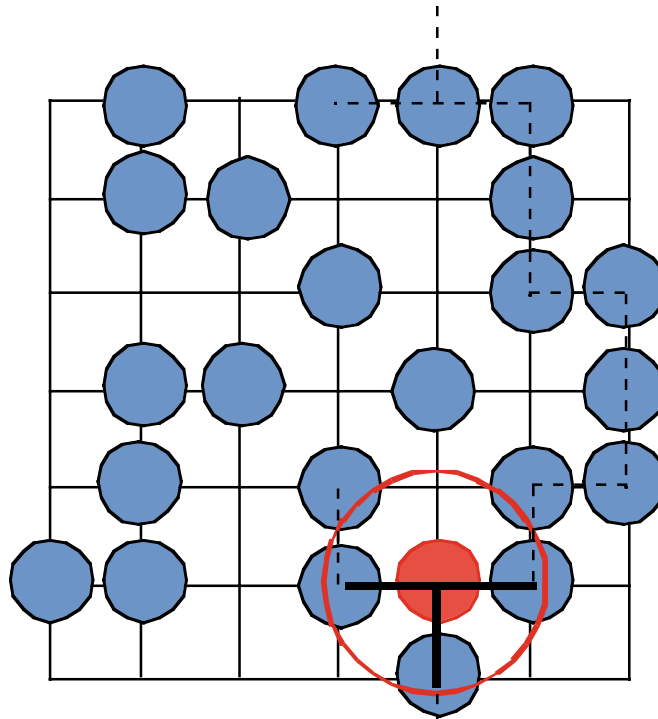
-391 kcal/mol  
 -1020 kcal/mol

# clustering...



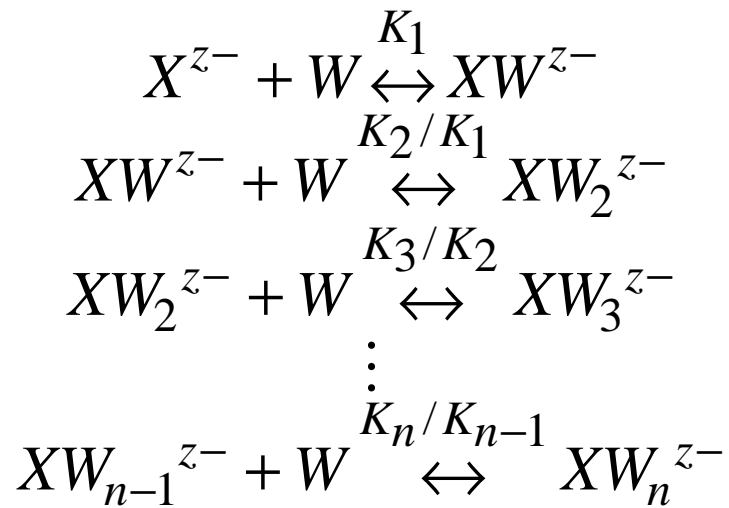
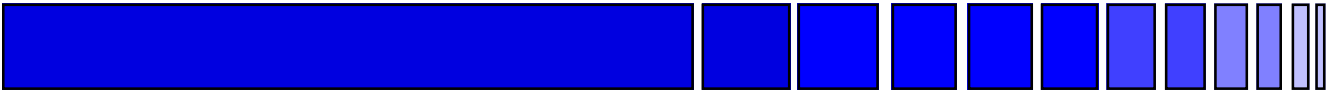
## ■ local (not spanning) clusters

- “Quasi-chemical theories of associated liquids,” Pratt & LaViolette, LA-UR-98-991 (*Molec. Phys.* 1998 in press)



- “One of the principal objects of theoretical research in my department of knowledge is to find the point of view from which the subject appears in its greatest simplicity.” J. W. Gibbs

# Quasi-chemical formulation



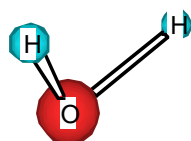
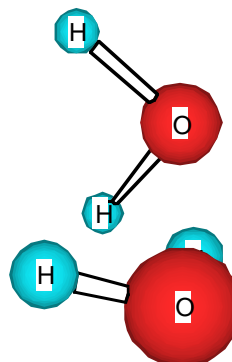
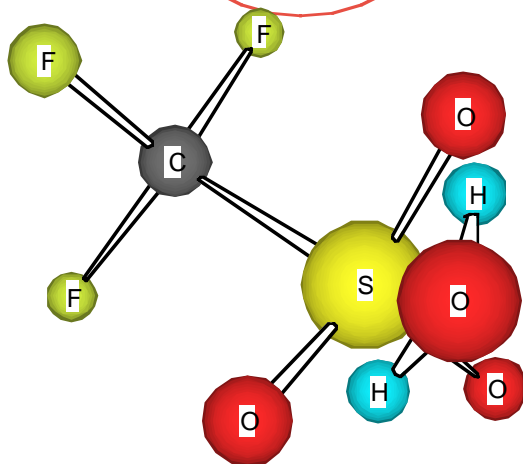
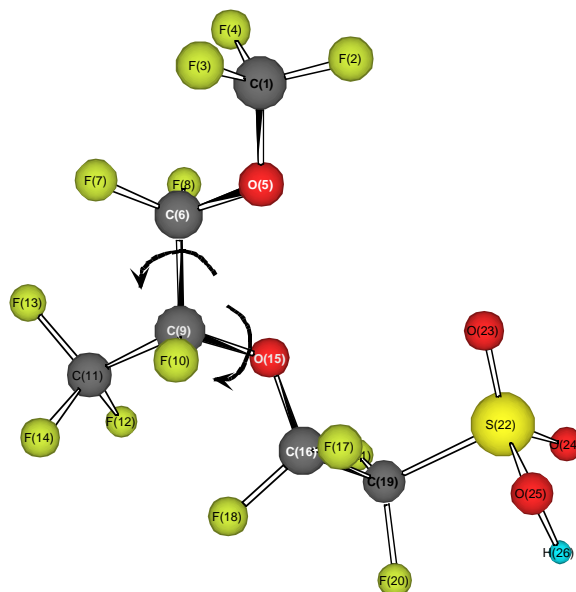
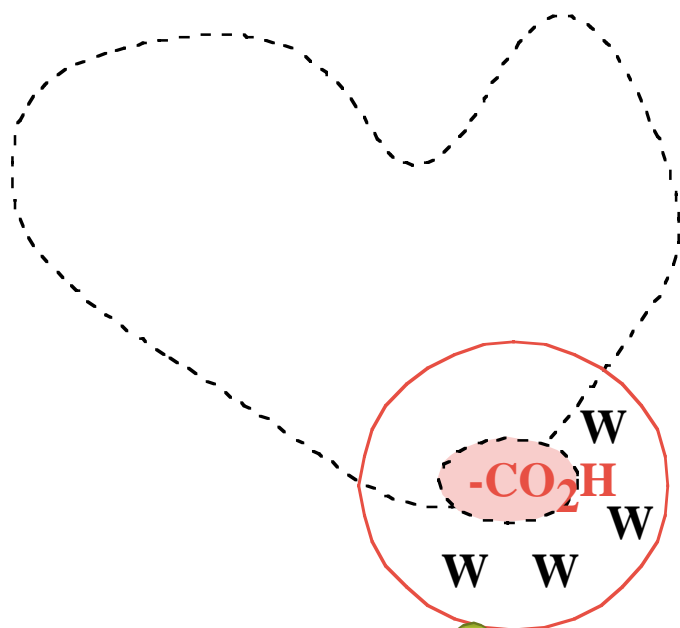
$$\begin{aligned}
 \mu_{X^{z-}} = & RT \ln \left[ \frac{\rho_{X^{z-}}}{(q_{X^{z-}} / V)} \right] \\
 & - RT \ln p_0 \\
 & - RT \ln \left[ \sum_{n=0} \tilde{K}_n \rho_W^n \right]
 \end{aligned}$$

ideal,

packing,  
chemistry ,  
electrostatics,  
entropy.

- $p_0$ =probability of an open cavity for the cluster volume, *e.g.* (1- $\rho v$ ), entropy too.

# extended (macromolecules)?



# Conclusions: Implicit models + first solvation shell



- **Dielectric models for hydration breakdown first because of near neighbor protons that lead to non-gaussian fluctuations of electrostatic potentials.**
- **Explicit consideration of near neighbor water molecules as in multi-gaussian models repairs (except, perhaps for negative ions) this primary failure of dielectric models.**
- **Quasi-chemical approaches again treat near neighbor water molecules specially but permit straightforward application of electronic structure calculations on inner solvation shells. This should also fix problems with negative ions.**